MERCK SHARP & DOHME LTD *GB 2347423-A

1999.03.02 1999-004786(+1999GB-004786) *(2000.09.06)* C07D 211/20, A61K 31/445 // A61P 25/00 (A61P 29/00)

New piperidine derivatives, useful for treatment of e.g. pain, inflammation, migraine, emesis and post-herpetic neuralgia, are tachykinin and particularly substance P antagonists

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Addnl. Data: MACLEOD A M, SWAIN C J, VAN NIEL M B

2000.02.22 2000GB-004167.

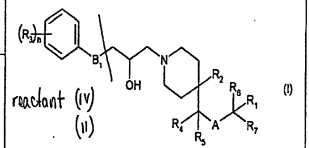
NOVELTY

Piperidine derivatives (I) are new.

DETAILED DESCRIPTION

Piperidine derivatives of formula (I) and their salts and prodrugs are new.

B(6-H, 7-D5, 14-C1, 14-C3, 14-C9, 14-E1, 14-E5, 14-E8, 14-E10, 14-E10C, 14-E11, 14-F1B, 14-F2, 14-G2A, 14-G2C, 14-H1, 14-J1A1, 14-J1A3, 14-J1A4, 14-J1B3, 14-J1B4, 14-J5, 14-J7, 14-K1, 14-K1A, 14-L6, 14-M1, 14-N3, 14-N7B, 14-N16, 14-N17, 14-N17A, 14-S1) .13



R_1, R_2 = phenyl (optionally substituted by 1-3 1-6C alkyl, 2-6C alkenyl, 2-6C alkynyl, 3-7C cycloalkyl, (3-7C cycloalkyl)(1-4C alkyl), 3-7C cycloalkoxy, 1-6C fluoroalkyl, 1-6C alkoxy, 1-6C fluoroalkoxy, OH, phenoxy, halogen, CN, NO_2, SR_a, SOR_a, SO_2R_a, NR_aR_b, NR_aCOR_b, $NR_aCO_2R_b$, COR_a, CO_2R_a or $CONR_aR_b$;

R_3 = halogen, CN, NO_2, 1-8C alkyl, 2-6C alkenyl, 2-6C alkynyl, 3-7C cycloalkyl, (3-7C cycloalkyl)(1-4C alkyl), 3-7C cycloalkoxy, 1-6C fluoroalkyl, 1-6C alkoxy, 1-6C fluoroalkoxy, OH, 1-6C hydroxyalkyl, 1-6C hydroxyalkoxy, SR_a, SOR_a, SO_2R_a, NR_aR_b, NR_aCOR_b, $NR_aCO_2R_b$, COR_a, CO_2R_a, $CONR_aR_b$, adamantyl, morpholinyl (optionally substituted by 1 or 2 1-4C alkyl) or phenyl, phenoxy, phenylazo, benzyl or benzyloxy (all optionally ring-substituted by one or two halogen, 1-4C alkyl, 1-4C alkoxy or OH); or

R_3+R_3 on adjacent C = OCH_2O, OCH_2CH_2O, $CH_2CH_2CH_2$, $CH_2CH=CH$, $NR_aCH=CH$ or $OC(R_a)_2CO$;

R_4-R_7 = H or 1-6C alkyl;

R_a, R_b = H, 1-6C alkyl, phenyl or CF_3;

A = O or S;

B_1 = O, S, NR_a or CHR_a; and

n = 0-5.

An INDEPENDENT CLAIM is included for the preparation of (I).

ACTIVITY

Analgesic; antiinflammatory; antimigraine; antiemetic; antidepressant; eating disorders; antiasthmatic; antiarthritic; osteopathic; antirheumatic; vulnerary; tranquilizer; neuroleptic; nootropic; antiparkinsonian; antimicrobial; neuroprotective; muscular; antiaddictive; antialcoholic; antismoking; endocrine; anticonvulsant; vasotropic; cerebroprotective; respiratory; gastrointestinal; antipsoriatic; antiallergic; cytostatic; ophthalmological; antiulcer; antacid; immunosuppressive; dermatological; uropathic; antianginal

MECHANISM OF ACTION

Tachykinin antagonist; Substance P antagonist; mucolytic. CHO cells stably expressing the human NK-1 receptor were incubated with (I) and [^{125}I]-Tyr^{8}-substance P at room temperature until equilibrium is achieved and the receptor-ligand complexes and then harvested by filtration on GF/C filters soaked in polyethyleneimine. (I) showed IC_{50} of < 100 nM, preferably < 10 nM.

USE

For treatment of a disorder associated with an excess of tachykinins, particularly pain, inflammation, migraine, emesis or post-herpetic neuralgia (claimed). Also for treatment of depression, dysthymic disorders, depressive neuroses, anorexia, seasonal affective

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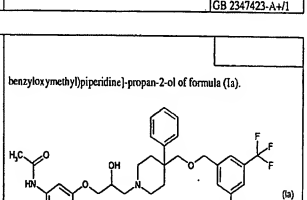
disorder, asthma, osteoarthritis, rheumatoid arthritis, burns, anxiety disorders, schizophrenia, delirium, dementia, amnesia, Alzheimer's disease, Parkinson's disease, Creutzfeld-Jakob disease, movement disorders, substance related disorders due to drugs, alcohol and nicotine such as dependence and withdrawal, psychotic disorders, sleep disorders, sexual dysfunction, epilepsy, Down's syndrome, demyelinating diseases, cerebral vascular disorders, respiratory disorders, cystic fibrosis, inflammatory bowel disease, psoriasis, allergies, hypersensitivity disorders, ophthalmic disorders, cancer, gastric disorders, gastritis, ulcers, acid indigestion, dyspepsia, transplant rejection, systemic lupus erythematosus, sclerodcrma, cystitis, angina and Raynaud's disease.

ADVANTAGE

Strongly inhibitory for tachykinins without the side effects of prior art drugs such as benzodiazepines.

SPECIFIC COMPOUNDS

Ten compounds are specifically claimed, e.g. 3-(3-acetamidophenoxy)-1-[4-phenyl-4-(3,5-bis-trifluoromethyl-benzyloxymethyl)piperidine]-propan-2-ol of formula (Ia).



(Ia)

ADMINISTRATION

Dosage is 0.001-50 (0.05-10) mg/kg/day. Administration is oral, parenteral, nasal, sublingual or rectal or by inhalation or insufflation.

EXAMPLE

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(con't)

3-Ethylphenol (1.50 g) was dissolved in 1N sodium hydroxide and epichlorohydrin (2.07 g) added and the mixture stirred at room temperature for 4 days. Excess epichlorohydrin was removed by concentration *in vacuo* and the two phase mixture treated with tetrahydrofuran (10 ml) and 1N sodium hydroxide (10 ml). The mixture was heated to 55 ° C for 15 minutes and then stirred at room temperature for 30 minutes, followed by removal of tetrahydrofuran by *in vacuo* concentration. The product was extracted with ethyl acetate (2 × 50 ml), concentrated *in vacuo* and purified by flash column chromatography on silica (using 150:10:1 dichloromethane:methanol:ammonia as eluant) to give 3-ethylphenoxy-oxirane as a yellow oil.

Of this product, 200 mg was dissolved in isopropanol (10 ml) and refluxed with 4-phenyl-4-[3,5-bis-(trifluoromethyl)-benzyloxymethyl]piperidine (375 mg) for 16 hours. The mixture was concentrated *in vacuo* to a yellow oil which was purified by flash column chromatography on silica using the same elution mixture as the previous step to give 3-ethylphenoxy-1-[4-phenyl-4-[3,5-bis-(trifluoromethyl)-benzyloxymethyl]piperidine]propan-2-ol as a yellow oil.

This product could be optionally converted to the oxalate salt by dissolution in diethyl ether and addition of 1 equivalent of oxalic acid.

DEFINITIONS

Preferred Definitions:

A, B_1 = O; and

R_1-R_7 = H.

TECHNOLOGY FOCUS

Organic Chemistry - Preparation; Claimed preparation of (I) is by one of 3 methods, i.e.:

(A) by reaction of an epoxide of formula (II) with a 4,4-disubstituted piperidine derivative of formula (III);

(B) for (I) where B is other than CHR_x, by reaction of phenyl derivative of formula (IV) with an 1-epoxymethylpiperidine derivative of formula (VI) in the presence of a base; or

(C) for (I) where B = CHR_x, by reaction of an 1-epoxymethylpiperidine derivative of formula (VI) as above with an organometallic benzyl derivative of formula (VII).

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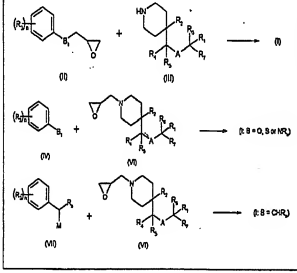

M = Li or MgHal; and

Hal = Cl, Br or I.

Each of the above processes may be followed by one or more of removal of any protecting groups, optical resolution and/or conversion to salt form

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